REMARKS

Enclosed herewith as part of the Substitute Specification and in full compliance with 37 C.F.R. §§1.821-1.825 is a Substitute Sequence Listing. The Substitute Sequence Listing in no way introduces new matter into the specification. Also submitted herewith in full compliance to 37 C.F.R. §§1.821-1.825 is a disk copy of the Substitute Sequence Listing. The disk copy of the Sequence Listing, file "new1614-0244P.ST25", is identical to the paper copy, except that it lacks formatting.

Reconsideration of this Application is respectfully requested.

Upon entry of the present amendment, claims 6-21 will remain pending in the application. These amendments do not introduce new matter, and their entry is respectfully requested.

In the Office Action of December 4, 2001, the Examiner set forth a number of grounds for rejection. These grounds are addressed individually and in detail below.

Restriction/Election

Applicants acknowledge that the Examiner has previously set forth a restriction requirement and withdrawn claims 7-11 and 13-14 from further consideration. Applicants elected, with traverse, claims 1-6 for continuing prosecution.

Objections to the Specification and drawings

In the Office Action, the disclosure is objected to because of numerous informalities. Applicants have complied with the Examiner's suggestion and made corrections in the enclosed Substitute Specification. No new matter was added. A clean version and a marked-up version are provided.

Claim Objections

Claim 3 stands objected to because the word "the" is recited twice in the claim. Applicants have cancelled claim 3 rendering this objection moot.

Rejections under 35 U.S.C. § 112, First Paragraph

Written Description

Claims 1-6 stand rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter that was not described in the specification in such a way as to demonstrate to one skilled in the art, at the time the application was filed, that the inventors had possession of the claimed invention. The Examiner states that the specification does not disclose a full-length amino acid sequence of recombinant Phl p6 allergen while the full-length amino acid sequence of Phl p6 is required to practice the instant

invention. Applicants address this issue as it applies to the present claims.

The full-length sequence of the recombinant Phl p6 is disclosed in the specification on page 9, lines 25-27, by referring to a deposition in the GenBank database, accession numbers Y16955-Y16960. These Accession numbers can also be found in ref. 37 of the application, "Vrtala S. et al., J. Immunol. 163:5489-5496 (1999)", on page 5492. Applicants have amended the specification to include a sequence listing showing the full-length sequence of recombinant Phl p6 allergen and portions thereof previously described. No new matter is added by these amendments. The filing date of the application should not be affected. MPEP § 608.01(p)(2).

The amendment of the specification completely addresses the stated grounds of rejection. Thus, the rejection of claims 1-6 for lack of written description should be withdrawn.

Enablement

The Examiner further cites the reference of Mohapatra et al. to argue that there is insufficient guidance as to which amino acid residues may be deleted to make a Phl p6 molecule which "at least substantially lacks IgE binding capacity."

The reduced IgE binding capacity is disclosed in the specification. Fig. 1 shows clones (e.g. 121, 146 and 233) with

strongly reduced IgE binding capacity. The sequences of these clones are now included in the specification. These data would enable one reasonably skilled in the art to practice the invention without undue experimentation.

According to *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), there are many factors to be considered when determining whether the specification provides enabling disclosure or whether any necessary experimentation is "undue." These factors include, but are not limited to:

(A) The breadth of the claims;

(B) The nature of the invention;

(C) The state of the prior art;

(D) The level of one of ordinary skill;

(E) The level of predictability in the art;

(F) The amount of direction provided by the inventor;

(G) The existence of working examples; and

(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

In re Wands, 858 F.2d 731, 737, (Fed. Cir. 1988).

It is improper to conclude that a disclosure is not enabling based on an analysis of only one of the above factors while ignoring one or more of the others. The examiner's analysis must consider all the evidence related to each of these factors, and any

conclusion of non-enablement must be based on the evidence as a whole. *Id* at 1404, 1407.

With regard to the above described factors (factor A-H), the instant invention claims Phl p6 molecules with N-terminal or C-terminal deletions that abolish the IgE binding capacity of the peptides, as well as pharmaceutical compositions comprising such molecules. Claim 6 recites two such molecules in combination. Claims 15-16, 18-20 are directed to a polypeptide having particular sequence and so should be free of this ground of rejection. Claim 17 and 21 list three enumerated peptides as one ingredient of the combination of claim 6.

The nature of the invention relates to the use of molecular biological techniques to overcome problems in the field of immunology. In particular, peptide compositions useful for desensitization therapy that have the advantage of not triggering an allergic response and their use are claimed.

In this field, the person of ordinary skill in the art typically has a Ph.D. degree and some working experience in protein chemistry, molecular biology and immunology.

The state of the art is established by the periodical literature. Applicants enclose the following references: Frank R. *J. Biotech.* 41:259-272, (1995); Gill, I. et al., *Enzy and Micro Tech.* 18:162-183, (1996); Scheiner O et al., Arbeiten aus dem Paul-Ehrilich-Institute (1994); and Valenta et al., *Clin and Exper*

Aller. 29:896-904, (1999).

Methods of making variant protein molecules were well known in the art at the time of the invention was made. [Frank R. *J. Biotech*. 41:259-272, (1995); Gill I et al., *Enzy and Micro Tech*. 18:162-183, (1996)] Mapping peptides to determine especially immunodominant epitopes was a well-established method [Scheiner O et al., Arbeiten aus dem Paul-Ehrilich-Institute (1994)]. Assays for IgE binding were well known in the art [Valenta et al., *Clin and Exper Aller*. 29:896-904, (1999)]. The complete amino acid sequence of the Phl p6 protein of at least one species of grass was known, as shown by prior art cited by the Examiner.

Furthermore, the present specification teaches how to construct and express Phl p6 fragments in a recombinant expression system. The present application discloses the complete amino acid sequence of Phl p6 and demonstrates, as working examples, that C-terminal-deleted Phl p6-derivative aa 1-57, and N-terminal-deleted Phl p6-derivatives aa 31-110 (c121), aa 54-110 (c233), and aa 58-110 (c146) lack IgE binding activity. The specification further provides detailed description on how to generate truncated Phl p6 molecules and how to screen such molecules for IgE binding activity (e.g. by immunoblot inhibition or histamine release assay).

As to the element of predictability, the Examiner takes a position that the practitioner of the invention must be able to predict, *a priori*, a structure of a Phl p6 peptide that lacks IgE

binding activity. However, this is not the proper viewpoint from which to assess predictability. It is not necessary for one skilled in the art to know before conducting any experimentation the exact structure of a peptide that lacks IgE binding activity to practice the present invention. Rather, a skilled artisan only needs to expect that he can generate a number of candidate peptides using the information and technology disclosed in the specification and screen these peptides to obtain those that lack IgE binding activity.

In *Wands*, the applicants screened hybridoma cell lines for production of antibody necessary to practice invention. Only 4 out of 143 hybridomas, or 2.8 percent, were proved to fall within the claims. Furthermore, antibodies that were proved to be high-affinity IgM came from only 2 of 10 fusion experiments. These statistics are viewed by the Board of Patent Appeals and Interferences as evidence that Wands' methods were not predictable or reproducible. The Court of Appeals Federal Circuit, however, concluded that the board's interpretation of the data was erroneous. The Court recognized that practitioners of monoclonal antibody technology are prepared to screen hybridomas with desired characteristics, and that it would not require undue experimentation to obtain antibodies needed to practice the claimed invention. The Court further concluded that the sole issue on enablement is whether it would require undue experimentation to

produce requisite antibodies using applicants' method. In this regard, the court stated that the key word is "undue", not "experimentation", and found that, in an art where screening embodiments for a desired activity is expected experimentation, such screening is not undue experimentation. *Id.* at 1404.

Based on the disclosure of the specification, one skilled in the art learns that both the C-terminal and N-terminal of the Phl p6 are required for IgE binding and that the N-terminal amino acid residues responsible for IgE binding are located within the first 31 residues. With the guidance as to structure and function (with respect to IgE binding) provided by the inventor and the general knowledge of how to assess the various functions of a peptide provided by the state of the art, one skilled in the art would only need to create various truncated Phl p6 constructs and perform routine screening to obtain Phl p6-derivatives with reduced IgE binding activity. As indicated by the *Wands* court, "enablement is not precluded by the necessity for some experimentation such as routine screening." *Id.* at 1404.

Taken together, applicants respectfully submit that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation.

It is believed that the grounds for this rejection have been

obviated, and therefore the rejection under 35 U.S.C. § 112, first paragraph, for alleged lack of enabling disclosure, should be withdrawn.

Rejections under 35 U.S.C. § 112, Second Paragraph

Claims 1-6 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. The Examiner states that the term "substantially" in claims 1 and 6, and the term "encompass the complete sequence of Phl p6" in claim 6 is unclear.

Applicants have cancelled claims 1-5 and deleted the word "substantially" from claim 6. Claim 6 has also been amended to replace the word "encompass" with the word "span". Accordingly, it is believed that the grounds for this rejection have been obviated, and may properly be withdrawn.

Rejections under 35 U.S.C. § 102

Claims 1 and 3-5 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Petersen et al.(Int Arch Allergy Immunol 1995, 108:55-59). Claims 1-5 have been canceled. The rejection is now moot.

Claims 1-6 further stand rejected under 35 U.S.C. § 102(a) as being anticipated by WO 99/34826. WO 99/34826 teaches a method for induction of T-cell tolerance by using synthetic peptides of the major cat allergen. WO 99/34826 also teaches this use of N-terminal

deleted Phl p6-derivatives and a few Phl p6-derived peptides per se.

Claims 1-5 have been canceled. With regard to claim 6, Applicants respectfully traverse the rejection. WO 99/34826 does not teach any combination of N-terminal deleted and C-terminal deleted Phl p6 peptides as described in claim 6 of the instant application. WO 99/34826 neither discloses nor suggests to select the N-terminal deleted Phl p6 peptide (SEQ ID NO: 20) of claims 15-16 and the C-terminal deleted Phl p6 peptide (SEQ ID NO: 21) of claims 118-21.

Applicants thus respectfully submit that the claimed invention is not anticipated by WO 99/34826 and withdrawal of 35 U.S.C. § 102 rejection is respectfully requested.

Accordingly, in view of the above amendments and remarks, reconsideration of the rejections and allowance of the claims of the present application is respectfully requested.

CONCLUSION

All of the stated grounds for rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding rejections and that they be withdrawn. It is believed that a full and complete response has been made to the outstanding Office Action and, as such, the present application is in condition for allowance.

Prompt and favorable consideration of this Response is respectfully requested.

Attached hereto is a marked-up version of the changes made to the application by this Amendment.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Ping Wang, M.D. (Reg. No. 48,328) at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

Pursuant to the provisions of 37 C.F.R. §§ 1.17 and 1.136(a), the Applicants hereby petition for an extension of two (2) months to May 4, 2002 in which to file a reply to the Office Action. The required fee of $400.00 is enclosed herewith.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. §§ 1.16 or 1.17; particularly, extension of time fees.

Respectfully submitted,

BIRCH, STEWART, KOLASCH & BIRCH, LLP

By mfp Nell #36,623
Gerald M. Murphy, Jr., #28,977

P.O. Box 747
Falls Church, VA 22040-0747
(703) 205-8000

GMM/PW/end
1614-0244P

Attachments: Version with Markings to Show Changes Made
(1) Frank R. *J. Biotech.* 41:259-272, (1995)
(2) Gill, I. et al., *Enzy and Micro Tech.* 18:162-183, (1996)
(3) Scheiner O et al., Arbeiten aus dem Paul-Ehrilich-Institute (1994)
(4) Valenta et al., *Clin and Exper Aller.* 29:896-904, (1999)

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION:

A marked-Up Substitute Specification is submitted herewith.

IN THE CLAIMS:

Claims 1-5 have been cancelled.

The claims have been amended as follows:

6. (Amended) A hypoallergenic immunogenic combination of molecules derived from the Phl p 6 allergen, comprising (i) a Phl p 6 molecule having an N-terminal deletion which makes the molecule at least [substantially] lack IgE binding capacity, and (ii) a Phl p 6 molecule having a C-terminal deletion which makes the molecule at least [substantially] lack IgE binding capacity, which two molecules together [encompass] span the complete sequence of Phl p 6.

Claims 15-21 have been added.